THIOURACIL TREATMENT OF THE FEMALE GUINEA PIG: EFFECT ON REPRODUCTION AND THE OFFSPRING

by

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INTRODUCTION

Since 1926, when Litzenberg suggested that basal metabolisms of minus 10 or lower are apparently a cause, or the index of a cause of sterility, the opinion has been generally held that even lesser degrees of hypofunction of the thyroid gland have an effect on reproduction in man. Breckinridge (1932) relates hypothyroidism to amenorrhea, menorrhagia, premature labor and abortion. Frazier and Ulrich (1932) state that hypothyroidism in pregnant women may cause abortion, and that if living babies are born, they may be cretins. Davis (1935) and King and Herring (1939) found that a low basal metabolism was associated with many gynecologic problems. Among these were uterine hemorrhage, repeated abortion and premature labor. Both found that feeding dessicated thyroid allowed several habitual aborters to carry pregnancy to term. Mussey (1938) found that amenorrhea is commonly associated with a low basal metabolism. Fluhmann (1941) reports that a secondary amenorrhea frequently accompanies a hypothyroid condition.

That the hypothyroid state is not always associated with impaired reproductive performance is indicated by Veil's (1917) and Parkin and Green's (1942) reports of pregnancy in myxedematous women, and Baumgartner's (1942) statement: "Although the incidence

of sterility is high among hypothyroid women, the fact remains that they can become pregnant." Peters, Man and Heinemann (1948), using the blood iodine technique, found that a low precipitable serum iodine in early pregnancy often leads to early miscarriage. However, the level during pregnancy is not related to the level prior to pregnancy. Their results, therefore, give no support to the opinion that a thyroid deficiency is necessarily a cause of the failure of conception.

Investigation of the relationship between the hypothyroid state and reproductive performance in laboratory mammals and birds has yielded conflicting and confusing results, although the bulk of the evidence suggests that in other species, as in man, reproduction may be impaired by a lowered level of thyroid activity. Salmon (1936) reports that thyroparathyroidectomy of female rats at birth brought about an arrest of the developing ova at partial antrum formation. Hammett (1922) found that thyroparathyroidectomy of female rats prior to puberty delayed the occurrance of the first pregnancy, reduced the litter size and increased the mortality at birth. Elsewhere (Hammett, 1926) he reports that operation at 100 days of age brought about a great decrease in ovarian size, but that ovaries are more resistent to the effects of thyroparathyroidectomy at the 75th day than when the operation takes place on the 100th day. Allowance for the possible effect of a parathyroid deficiency

was not made in any of these studies, but even in other investigations, in which thyroidectomy alone was claimed, more often than not, effects attributed to the removal of the thyroid were reported.

Lee (1925) found that thyroidectomy of the female rat increased the length of the diestrum as measured by the vaginal smear technique. Freedman, Wright and Webster (1935) and Ross (1938), also working with the rat, described prolongation and irregularities in the vaginal cycles following thyroidectomy, while Evans and Long (1921) and Tobin (1942) observed temporary anestrum followed by normal cycles in the same species. Williams, Phelps and Burch (1941) found that thyroidectomy caused a failure of corpus luteum formation in the ovary of the guinea pig. Fredrickson and Rydin (1947) could detect no change in the action of ovarian hormones on the endometrium of the rabbit following thyroidectomy. In the primates, Engle (1944) reported menstrual irregularities in the rhesus monkey following thyroidectomy. Greenwood and Chu (1939), Winchester (1939) and Taylor and Burmeister (1940) all reported that thyroidectomy of the chicken reduced egg production.

The results of mating of thyroidectomized females with normal males have been similar to the observations on folliculogenesis and the character of the cycle to the extent that inconsistencies are numerous. Patterson, Nicodemus and Hunt (1938) found that

thyroidectomized rabbits died in the last trimester of pregnancy, while Krichesky (1939) reports living offspring born to the same species. Hammett (1922) and Ross (1938) indicated that some thyroidectomized rats gave birth to living offspring. Marza (1929) found that living young were born to thyroidectomized guinea pigs. The discovery of the anti-thyroid drugs gave impetus to a reopening of studies bearing on the relationship between hypothyroidism and reproduction. Again, however, the results cannot be said to be consistent. Hughes (1944) reports an arrest of development and a cretinous appearance in rats treated with thiouracil from birth. Goddard (1948) found that rats treated with thiouracil from the 11th through the 112th day of age were somewhat dwarfed but did not differ from normal animals of the same age in general health, development and sexual maturation. Mayer's (1947) results suggest even less of an effect on beagle puppies; there was no delay in the development of the ovaries of animals treated with thiouracil from the 5th or 6th week until they were 6½ months old, and their growth was normal. Treatment with thiouracil did not interfere with folliculogenesis in the rat or guinea pig, (Hughes, 1944; Goldsmith, Gordon and Charipper, 1945; Seegar-Jones, Delfs and Foote, 1946; Albrieux, Estefan and Gonzales, 1946) because such animals became pregnant when mated with normal males. On the other hand, there are indications

that treatment with thiouracil may perhaps have an effect on follicular development, because Mann (1945) states that in female rats so treated there was an increase in the intervals between cornification of the vaginal mucosa, and Aranow, Engle and Sperry (1946) found that treatment of the rhesus monkey with thiouracil for 14 months caused menstrual irregularities with frequent periods of amenorrhea.

When the effect of thiouracil feeding on the course of pregnancy was studied (Hughes, 1944; Goldsmith, Gordon and Charipper, 1945; Seegar-Jones, Delfs and Foote, 1946; Albrieux, Estefan and Gonzales, 1946), it was found that treatment from 4 to 49 days prior to mating did not interfere with the delivery of living offspring. There is, however, disagreement with respect to the effect of longer treatment. Seegar-Jones, Delfs and Foote (1946) reported 100 per cent resorptions in rats treated 134 days or longer, but Hughes (1944) found that living offspring were delivered to females treated 8 to 10 months before mating occurred.

Hyperplasia of the fetal thyroid followed thiouracil treatment of pregnant female rats (Hughes, 1944; Goldsmith, Gordon and Charipper, 1945) and guinea pigs (Albrieux, Estefan and Gonzales, 1946). Andrews and Schnetzler (1945) reported hyperplasia of the thyroid glands in chicks from thiouracil treated hens. Davis and Forbes (1945) found a hyperplastic thyroid gland in an

infant born to a woman treated with thiouracil for thyrotoxicosis, but Whitelow (1947) saw no hyperplasia of the thyroid in a fetus from another woman undergoing similar treatment.

Because so many of the results reported by other investigators are contradictory and, at the time this study was begun, no one had as yet determined the effect of thiouracil-induced hypothyroidism in the guinea pig, the experiments to be described were undertaken. While this work was progressing, the article of Albrieux, Estefan and Gonzales (1946) appeared, in which it was stated that treatment of female guinea pigs starting the 10th day of pregnancy did not produce apparent modifications in its course, and that either thiouracil or the thyrotrophic hormone passed through the placenta to cause hyperplasia of the fetal thyroid gland. These results were confirmed in the present investigation. In several respects, though, additional information was obtained and the data, therefore, are reported in their entirety.

MATERIALS AND METHODS

Three groups of adult female guinea pigs were fed 6-propyl-thiouracil. Group I was composed of 38 animals in which treatment was begun from 38 to 219 days prior to mating with normal males and continued throughout gestation and lactation. Seven females, constituting Group II, were placed on thiouracil the day of mating and treated throughout gestation and lactation. Six females in Group III were fed thiouracil during the balance of pregnancy, beginning the 38th day after mating. The animals in Group III were used in an experiment designed to give information with respect to the possibility of transplacental passage of thiouracil. Six animals were kept in a cage and 25 cc. of a 0.1 per cent solution of thiouracil was placed in the drinking water. Each animal, therefore, received an estimated dose of 25 mgms. daily, although variations, which depended on the amount of water consumed, must have existed.

With the exception of six animals that were observed during the late fall and early winter when the temperature of the animal room was kept at 75°, all were kept in air conditioned rooms, where the temperature was maintained at 75° Fahrenheit in summer and about 70° in winter.

The animals in Group I were examined at least twice daily for estrus as described by Young, Dempsey,

Hagquist and Boling (1937). When found in heat, they were placed with normal males until copulation was observed. Beginning the 15th day, animals that had mated were examined for the condition of the vaginal membrane, until it was determined whether or not the mating had been fertile. Females found pregnant were watched daily until the termination of pregnancy, when the sex, weight and condition of the offspring and the length of gestation were recorded.

At the termination of observations, the thiouracil-fed females were sacrificed. The thyroid glands were weighed and fixed in Dawson's fluid. The ovaries were fixed in Bouin's fluid. Representative sections of the thyroid were stained with hematoxylin and eosin and Mallory's triple stain. The thyroids from all the stillborn young and some living offspring obtained from the females in Group I were prepared similarly and studied microscopically. The ovaries from eight animals in Group I were serially sectioned and stained with hematoxylin and eosin.

Electrocardiograms were made to determine the heart rate of goitrous newborn offspring born to the females in Group III and of normal newborn animals. Oxygen consumption of experimental and normal newborn offspring was measured by means of a metabolism chamber similar to that described by Williams, Phelps and Burch (1941), but modified slightly by Mr. Roy Peterson

(unpublished report).

The weight of the young animals born to thiouracil-fed mothers and normal young was recorded daily for the first 14 days and monthly thereafter. Experimental and control animals were sacrificed at frequent intervals; at this time the thyroids were weighed, fixed and stained.

During the period of maturation, the female offspring were examined regularly for the appearance of estrus. When mature, they were mated with normal males and their fertility thus ascertained.

Six males born to thiouracil-fed mothers were placed in individual cages when they were 27 to 41 days old. In order to ascertain the age at which sexual maturation occurred, ten minute tests (Young, Webster and Wahlstedt, 1948) were made at approximately four-day intervals. Five normal males of similar age were also tested.

RESULTS

Adult females. The females fed thiouracil from 38 to 219 days prior to mating until the end of lactation showed no gross effects of thiouracil administration. The average weight at the time of sacrifice was 736 grams compared with 751 grams in untreated females of the same age (Table I). The amount of stored fat was normal. Macroscopically the thyroids were very hyperplastic, the average weight of 879.5 mgms. comparing with 163.6 mgms. in untreated females. The thyroids of females in Groups II and III showed no hyperplasia, the average weight being 118 mgms. in the former group and 124.7 mgms. in the latter (Table I). We cannot account for the lower weight of the thyroids from animals in these groups. The follicles in the thyroids from animals in Group I were lined by columnar cells and there was a trace of colloid in only one follicle in one gland (Fig. 1). In animals of Group II, cells lining the follicles were columnar, but colloid was still abundant. In those comprising Group III, no gross or microscopic effect of thiouracil feeding was seen by the method of examination employed.

There was no apparent effect on the estrous cycle. The females came into heat and the cycles were of normal length. Histological examination of the ovaries showed no abnormalities.

No mating in the females comprising Group I was

sterile. In 7 or 18.4 per cent of the 38 thiouracil-fed animals pregnancy was terminated prematurely. (Tentatively, any birth prior to the 60th day is regarded as premature). With the exception of two resorptions on the 28th and 31st days, the terminations of pregnancy that were premature occurred after the 50th day. In the remaining 31 animals, gestation was prolonged, having an average length of 70.3 days (Table II). Five of the 31 delivered stillborn litters, and 26 gave birth to living offspring. Lactation was of normal duration and sufficient to nourish the young.

There were no sterile matings among the females comprising Group II. There was a resorption on the 31st day and an abortion on the 56th day. Two animals gave birth to stillborn offspring and three to living young. The length of gestation was normal. Among the five animals in Group III, pregnancy in one was terminated prematurely with a resorption on the 31st day. In the others, gestation was of normal length and all gave birth to living offspring.

In 33 females comprising the control group no mating was sterile. Five or 15.1 per cent of the pregnancies were terminated prematurely and 3 of 28 litters were stillborn. The length of gestation averaged 67.9 days. It is clear, therefore, that except for its length, the course of gestation was not different in the treated and untreated animals.

Young born to thiouracil-fed females. Newborn offspring born to thiouracil-treated females differ in several respects from normal offspring. The most striking difference is the readily apparent bilateral swelling in the neck, caused by the greatly enlarged thyroid gland. The animals are quite inactive, and in many there is extreme muscular weakness. The fur is quite coarse in contrast to the soft fur seen in normal newborn offspring. The average weight at birth was eight grams more than that of normal animals (Table III). The average heart rate of six goitrous newborn young born to the females in Group III was 296.8 per minute compared with 399.8 per minute in six normal newborn (Table IV). The average oxygen consumption in cc. per 100 grams per hour was 221.3 in the goitrous newborn and 186.2 in the normal newborn (Table IV).

The macroscopic appearance of the thyroid glands of these animals is one of extreme hyperplasia and hyperemia (Fig. 2). Petechial hemorrhages are very common. The weight of these glands is much greater than those from normal newborn offspring, the average being 3491.6 mgms. compared with 35.5 mgms. (Table III). Microscopically, the stroma of the glands appears to be completely disorganized. There is no definite arrangement of the cells in follicles, instead, they form long irregular papillae, and no colloid is present (Fig. 3).

During the first 14 days after birth the animals gradually become more active and can no longer be distinguished from normal individuals with respect to activity, condition of the fur, and general appearance. The growth of such animals is similar to that of controls (Fig. 5) and by the fourteenth day much of the slight difference in weight at birth has disappeared.

There is a gradual regression in size of the thyroid. By the fourteenth day they are no longer palpable but are still larger than normal. By the fourth day the first trace of colloid appears and follicles are formed; such follicles are elongate and lined with columnar cells, but give the appearance of being organized (Fig. 6). By the fourteenth day the thyroid has enlarged follicles with colloid storage similar to that seen in mature animals born to thiouracil-fed mothers (Fig. 7).

By the 30th day body weight is within the range found in normal animals. The goitrous males averaged 307 grams compared with 298 grams in the normal males. The goitrous females averaged 294 grams compared with 295 grams in normal females (Fig. 5). At maturity, the weight of males and females born to thiouracil-fed mothers averaged 827 grams compared with 832 grams for the controls (Table VI).

Females goitrous at birth appear to show cyclic estrous activity as soon as normal females. After mating

with normal males, they give birth to normal offspring. Males goitrous at birth, when tested for the development of sex drive and fertility, achieved the first intromission at a somewhat earlier age than normal controls, the average being 42 days compared with 56 days in the latter group (Table V). First copulation with ejaculation occurred at the 52nd day in the males goitrous at birth, and at the 65th day in the controls. The difference between the two groups seen at the time of the first intromission and the first copulation with ejaculation had disappeared by the time of the first fertile copulation, the average age for the males goitrous at birth being 80 days, and for the controls 80.5 days.

The thyroid glands obtained from the adults at the termination of the experiment were still enlarged, the weight averaging 703.8 mgms. compared with an average of 149.5 mgms. in the controls (Table VI). Histologically, the glands presented an appearance of extreme colloid storage. The follicles were large and the cells lining them squamous. Epithelial spurs still protrude into the follicular lumina (Fig. 7). There was one exception. The thyroid from male 303 retained its fetal appearance and consisted of a few scattered irregular follicles containing colloid embedded in an abundant connective tissue stroma (Fig. 9). Notwithstanding, growth of this animal was normal and it had its first intromission and copulation with ejaculation on the 43rd day and its first

fertile mating on the 84th day which is within the normal range (Table V).

DISCUSSION

The results obtained in this investigation are in agreement with those reported by others who have studied the effect of thiouracil-induced hypothyroidism on reproduction in female laboratory mammals and who found that there is no effect on folliculogenesis that is incompatable with pregnancy (Hughes, 1944; Goldsmith, Gordon and Charipper, 1945; Albrieux, Estefan and Gonzales, 1946; Seegar-Jones, Delfs, and Foote, 1946). The principal disagreement has to do with the effect on fertility and the course of gestation as reported by Goldsmith, Gordon and Charipper (1945) and Seegar-Jones, Delfs and Foote (1946), following their studies of the rat. The former states that mixed litters maintained on thiourea for 7 months from the time of birth and prior to it delivered no offspring, while the latter report resorption of the fetuses in 100 per cent of the animals fed thiouracil 134 days or longer. Hughes (1944), on the other hand, states that living offspring were born to several adult female rats that had received the drug for 8 to 10 months previously. Inasmuch as pregnancy was carried to term in 31 of 38 female guinea pigs treated as long as 219 days before mating, comparison of the species must await a study that will reveal more definitely the effect of thiouracil feeding on the course of gestation in the rat.

It is generally felt that a hypothyroid condition brings about a premature termination of pregnancy in experimental mammals and man. Patterson, Nicodemus and Hunt (1938) found that abortion in the last trimester of pregnancy occurred in hypothyroid rabbits. Seegar-Jones, Delfs and Foote (1946) reported resorption of fetuses in the rat. Clinical reports would indicate that hypothyroidism in the human female is frequently associated with abortion (Davis, 1935; King and Herring, 1939). Since there is an average lengthening of gestation by two days in female guinea pigs treated with thiouracil for long periods prior to mating, it is apparent that the hypothyroid state in this species is not necessarily associated with the premature termination of pregnancy.

Transplacental passage of thiouracil is regarded as theprobable cause of hypertrophy of the fetal thyroid by Goldsmith, Gordon and Charipper (1944), Davis and Forbes (1945) and Albrieux, Estefan and Gonzales (1946). There are two possible means by which hyperplasia of the fetal thyroid might be induced. First, the thyrotrophic hormone from the mother might pass the placental barrier, and secondly, thiouracil might pass through and inhibit thyroid hormone formation by the fetal thyroid, with the result that the fetal thyrotrophic hormone acts to produce the goitrous glands. Females in which thiouracil was administered daily during the last 30 days of gestation still possessed thyroid glands which were normal in

appearance. As in the young born to mothers in which the period of treatment was much longer, the thyroids were consistently much enlarged. If it can be assumed from the large amounts of colloid in the follicles of the maternal thyroids that these glands were releasing thyroid hormone, the hypothesis would seem reasonable that thiouracil passed the placental barrier and induced the series of events leading to hyperplasia.

The rapid regression in size of the gland and the prompt appearance of colloid in animals goitrous at birth suggests that there is no transmammary passage of thiouracil in the guinea pig similar to that reported in the rat (Williams, Burch and Phelps, 1944; Goldsmith, Gordon and Charipper, 1945). The muscular weakness displayed at birth disappears rapidly and the growth rate is normal, which also discounts the likelihood of a transmammary effect.

The usual association of a high oxygen consumption with a fast heart rate was not seen in the goitrous animals for which these determinations were made. This lack of correlation between the oxygen consumption and the heart rate cannot be explained. Meyer and Thompson (1940), in a report on results obtained following the injection of different thyroid preparations into thyroidectomized rats, noted that at times these preparations raised the metabolic rate with only a slight increase in heart rate. They felt there was a possibility that the cardiac output was

maintained by an increase in stroke volume, rather than by a faster heart rate.

The results indicate that no permanent damage is brought about by hyperplasia of the fetal thyroid. It is true that the glands of mature animals in this group were larger than normal and had the appearance of colloid goitre. Notwithstanding, these animals maintained themselves at a level comparable with that of offspring from untreated females. Growth curves followed closely those of normal animals. There was no delay in sexual maturation in either the male or female, nor was there any lowering of fertility. It would seem that, if the thyroid gland has any effect on reproductive processes in the guinea pig, animals goitrous at birth can act efficiently at the level of thyroid activity they maintain.

The large goitres found in young born to thiouracil-fed mothers are puzzling. One might infer that there is an increased output of the fetal thyrotrophic hormone. On the other hand, the possibility cannot be excluded that the fetal thyroid is more sensitive to this hormone. In either case, the fetal thyroid is strongly stimulated and it is suggested that a high level of thyroid activity is somehow important for the fetus.

SUMMARY AND CONCLUSIONS

The effect of thiouracil-induced hypothyroidism on reproductive function in the female guinea pig was studied, as was the condition at birth and the subsequent development of young born to such females.

1. In the thiouracil-fed adult there were no abnormalities of folliculogenesis or of the reproductive cycle. Such animals conceived and gave birth to living young.

2. Pregnancy was not terminated prematurely in hypothyroid females, on the contrary, its average length was greater by two days.

3. The thyroid glands of newborn young delivered by thiouracil-fed females are very hyperplastic. Regression in size is rapid, but even after attaining adulthood the thyroid is about seven times larger than that in controls. Notwithstanding the goitrous condition at birth, and subsequently, the rate of growth and the time of sexual maturation are normal.

4. A transplacental passage of thiouracil in the female guinea pig is suggested.

5. There does not seem to be sufficient trans-mammary passage of thiouracil to maintain the goitrous condition of the young receiving milk from thiouracil-fed mothers.

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TABLE I

AVERAGE BODY AND THYROID WEIGHTS IN THIOURACIL-FED AND NORMAL FEMALES AT TERMINATION OF EXPERIMENT

	Number of animals	Age in days	Days on thiouracil	Body weight in grams	Thyroid weight in mgms.	Thyroid weight mgms./ 100 gms. body weight
Normal	12	341	0	736	163.6	22.8
Group I	12	353	106 to 287	751	879.5	121.8
Group II	6	343	68	746	118.0	15.6
Group III	1	340	30	720	124.7	17.3

TABLE II

LENGTH OF GESTATION IN NORMAL AND THIOURACIL-FED FEMALES

	Number of animals	Days on thiouracil	Range	Average	Average number in litter
Normal	28	0	65-70	67.9	3.0
Group I	31	106 to 287	67-72	70.3	3.0
Group II	5	68	62-70	66.9	3.0
Group III	4	30	64-70	67.8	2.4

TABLE III

AVERAGE BODY AND THYROID WEIGHT IN NORMAL NEWBORN

AND IN GOITROUS YOUNG FROM THIOURACIL-FED MOTHERS

	Number of animals	Body weight in grams	Thyroid weight in mgms.	Thyroid weight mgms./ 100 gms. body weight
Normal	15	74.6	35.5	46.9
Goitrous	15	82.6	3491.6	4224.8

TABLE IV

HEART RATE AS DETERMINED FROM THE ELECTROCARDIOGRAM AND OXYGEN CONSUMPTION IN CC. PER 100 GMS. PER HOUR IN GOITROUS AND NORMAL NEWBORN

Goitrous newborn males	Oxygen consumed	Heart rate per min.	Normal newborn males	Oxygen consumed	Heart rate per min.
1	247	276	1	186	430
2	220	240	2	218	412
3	240	318	3	171	390
4	202	300	4	181	389
5	207	324	5	175	378
6	212	323	6	186	---
Average	221.3	296.8	Average	186.2	399.8

TABLE V

AGE AT ATTAINMENT OF SEXUAL MATURITY

IN MALE GUINEA PIGS GOITROUS AT BIRTH

Control animals No.	Age in days at time of First intromission	First copulation with ejaculation	First fertile copulation
189L	62	66	84
208L	52	59	74
211L	40	56	83
215L	79	79	84
Average	56	65	80.5
Goitrous animals No.			
181L	50	50	89
303L	43	43	84
311L	43	63	76
341L	41	54	69
346L	40	57	72
360L	40	46	91
Average	42	52	80

TABLE VI

AVERAGE BODY AND THYROID WEIGHTS IN ADULT

THIOURACIL OFFSPRING AND NORMAL ADULTS

	Number of animals	Age in days	Body weight in grams	Thyroid weight in mgms.	Thyroid weight mgms./ 100 gms. body weight
Normal	15	236	832	149.5	17.9
Thiouracil	15	228	827	703.8	84.5

Figure 1. Thyroid gland from adult female fed thiouracil for 90 days. Note the hyperplasia and the presence of only a trace of colloid. x 300.

Figure 1

Figure 2. Low power photograph of a goitrous newborn male.

Figure 2

Figure 3. Thyroid gland of newborn goitrous offspring. Note lack of organization and absence of colloid. x 300.

Figure 4. Thyroid gland of normal newborn animal. x 300.

Figure 3

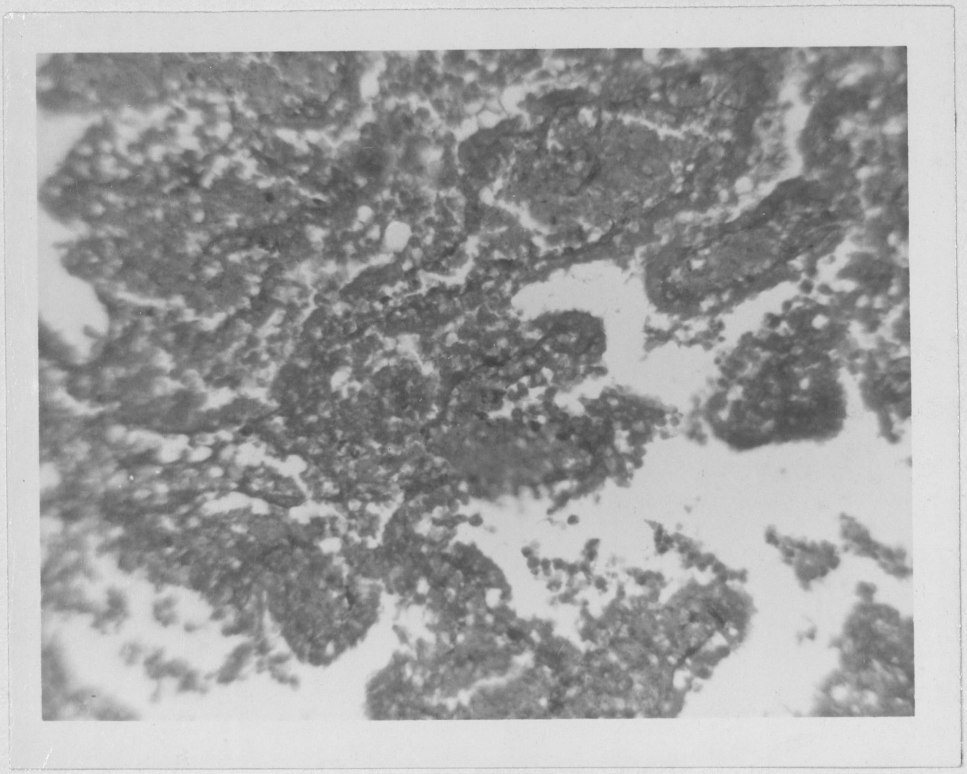

Figure 4

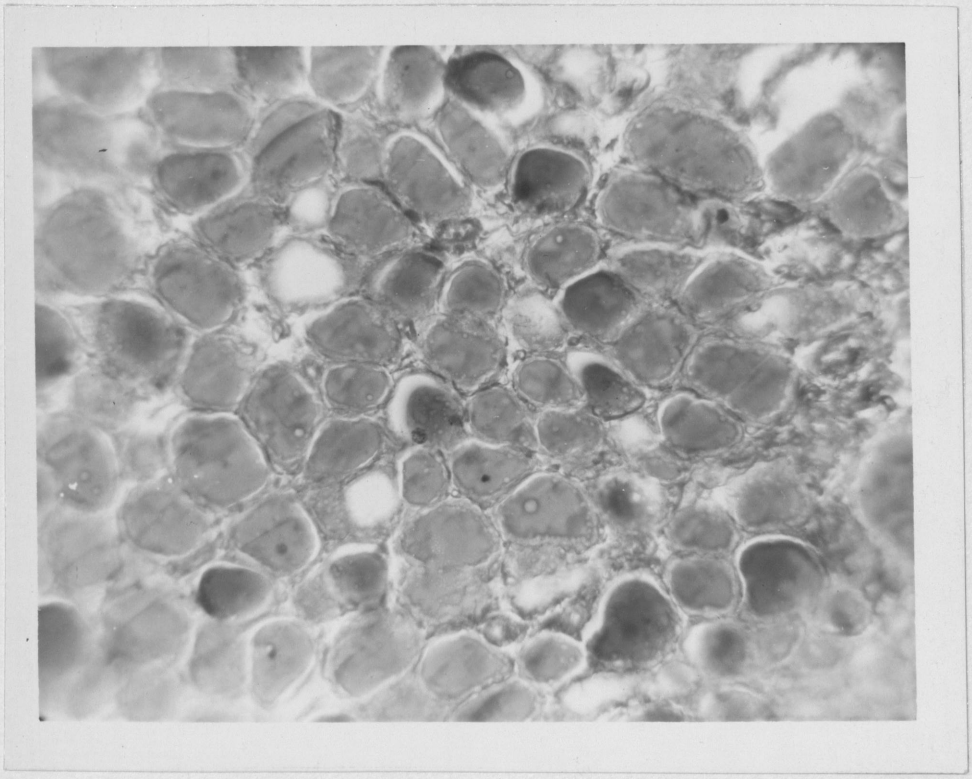

Figure 5

GROWTH CURVES OF ANIMALS GOITROUS AT BIRTH AND CONTROLS

FIFTEEN ANIMALS IN EACH GROUP

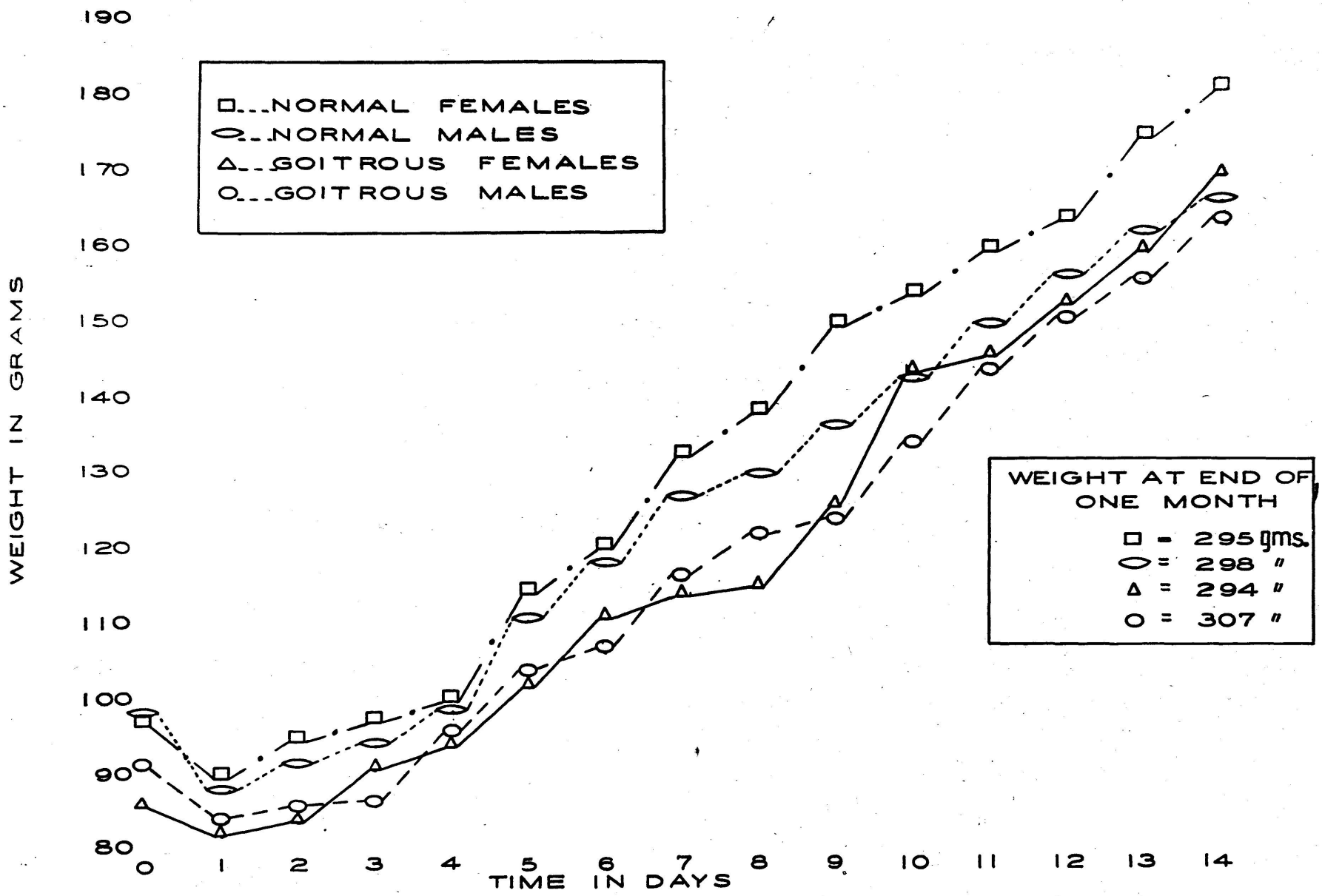

Figure 6. Thyroid gland of four day old thiouracil offspring. The gland shows organization into elongate follicles which are lined by columnar cells. Colloid is present in traces. x 300.

Figure 6

Figure 7. Thyroid gland of a 6 month old thiouracil offspring, with enlarged follicles and colloid storage. Note epithelial spurs. x 300.

Figure 8. Thyroid gland of a 6 month old normal animal. Note that the follicles are much smaller. x 300.

Figure 7

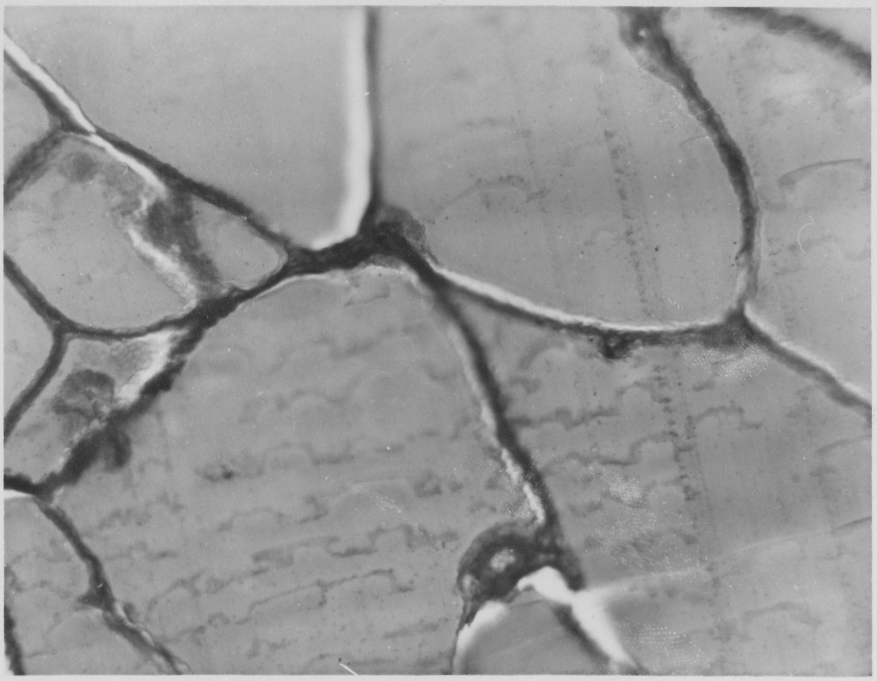

Figure 8

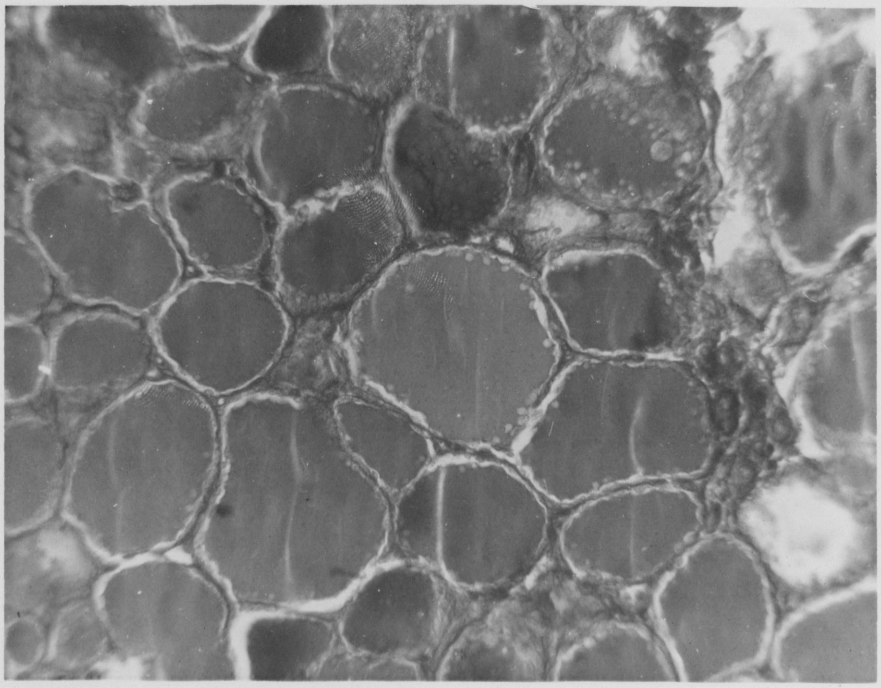

Figure 9. Thyroid gland of a 7 month old thiouracil offspring with a few scattered irregular follicles. This is an exception to the histological picture found in all other thiouracil offspring. x 300.

Figure 9